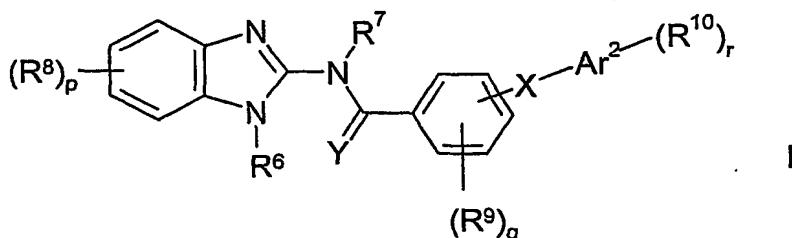


- 127 -

Claims

1. Benzimidazole derivatives of formula I

5



10

wherein

15 R^6, R^7 are independently from one another H, A or SO_2A ,

20

A is independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylene cycloalkyl, alkoxy and alkoxyalkyl,

25

Ar^2 is selected independently from one another from aromatic hydrocarbons containing 6 to 14 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 10 carbon atoms and one or two heteroatoms, independently selected from N, O and S,

30

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nOR^{11}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{12}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$,

- 128 -

(CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³,
 (CH₂)_nCOR¹³, (CH₂)_nSR¹¹, CH=N-OA, CH₂CH=N-OA,
 (CH₂)_nNHOA, (CH₂)_nCH=N-R¹¹, (CH₂)_nOC(O)NR¹¹R¹²,
 (CH₂)_nNR¹¹COOR¹², (CH₂)_nN(R¹¹)CH₂CH₂OR¹³,
 5 (CH₂)_nN(R¹¹)CH₂CH₂OCF₃,
 (CH₂)_nN(R¹¹)C(R¹³)HCOOR¹², C(R¹³)HCOR¹²,
 (CH₂)_nN(R¹¹)CH₂CH₂N(R¹²)CH₂COOR¹²,
 (CH₂)_nN(R¹¹)CH₂CH₂NR¹¹R¹², CH=CHCOOR¹¹,
 CH=CHCH₂NR¹¹R¹², CH=CHCH₂NR¹¹R¹²,
 10 CH=CHCH₂OR¹³, (CH₂)_nN(COOR¹¹)COOR¹²,
 (CH₂)_nN(CONH₂)COOR¹¹, (CH₂)_nN(CONH₂)CONH₂,
 (CH₂)_nN(CH₂COOR¹¹)COOR¹²,
 (CH₂)_nN(CH₂CONH₂)COOR¹¹,
 (CH₂)_nN(CH₂CONH₂)CONH₂, (CH₂)_nCHR¹³COR¹¹,
 15 (CH₂)_nCHR¹³COOR¹¹, (CH₂)_nCHR¹³CH₂OR¹⁴,
 (CH₂)_nOCN and (CH₂)_nNCO, wherein

20 R¹¹, R¹² are independently selected from a group consisting of H, A, (CH₂)_mAr³ and (CH₂)_mHet, or in NR¹¹R¹²,

25 R¹¹ and R¹² form, together with the N-atom they are bound to, a 5-, 6- or 7-membered heterocycloids which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S,

30 R¹³, R¹⁴ are independently selected from a group consisting of H, Hal, A, (CH₂)_mAr⁴ and (CH₂)_mHet,

Ar³, Ar⁴ are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group

- 129 -

consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,

5 Het is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_uA and OOCR¹⁵,

10 R¹⁵, R¹⁶ are independently selected from a group consisting of H, A, and (CH₂)_mAr⁶, wherein

15 Ar⁶ is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH₂ and CF₃,

20 k, m and n are independently of one another 0, 1, 2, 3, 4, or 5,

 X represents a bond or is (CR¹¹R¹²)_h, or (CHR¹¹)_h-Q-(CHR¹²)_l, wherein

25 Q is selected from a group consisting of O, S, N-R15, (CHal₂)_j, (O-CHR¹⁸)_j, (CHR¹⁸-O)_j, CR¹⁸=CR¹⁹, (O-CHR¹⁸CHR¹⁹)_j, (CHR¹⁸CHR¹⁹-O)_j, C=O, C=S, C=NR¹⁵, CH(OR¹⁵), C(OR¹⁵)(OR²⁰), C(=O)O, OC(=O), OC(=O)O, C(=O)N(R¹⁵), N(R¹⁵)C(=O), OC(=O)N(R¹⁵), N(R¹⁵)C(=O)O, CH=N-O, CH=N-NR¹⁵, S=O, SO₂, SO₂NR¹⁵ and NR¹⁵SO₂, wherein

30

- 130 -

R^{18} , R^{19} , R^{20} are independently selected from the meanings given for R^8 , R^9 and R^{10} , preferably independently selected from the group consisting of H, A, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, $(CH_2)_nOR^{11}$, $(CH_2)_nNR^{11}R^{12}$,
5 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$,
 $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
 $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$,
 $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nCOR^{13}$,
 $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$ and $(CH_2)_nNR^{11}COOR^{13}$,
10

h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and

j is 1, 2, 3, 4, 5, or 6,

15 Y is selected from O, S, NR^{21} , $C(R^{22})-NO_2$, $C(R^{22})-CN$ and $C(CN)_2$, wherein

R^{21} is independently selected from the meanings given for R^{13} , R^{14} and
20

R^{22} is independently selected from the meanings given for R^{11} , R^{12} ,

25 p, r are independently from one another 0, 1, 2, 3, 4 or 5,

q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,

u is 0, 1, 2 or 3, preferably 0, 1 or 2,

30 and

- 131 -

Hal is independently selected from a group consisting of F, Cl, Br and I;

and the physiologically acceptable derivatives, salts and solvates
5 thereof.

2. Benzimidazole derivative according to claim 1, wherein

10 Ar² is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,

15 R⁸, R⁹ and R¹⁰ are independently selected from a group consisting of H, A, cycloalkyl 3 to 7 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN, (CH₂)_nOR¹¹, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³, (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uR¹³, (CH₂)_nOC(O)R¹³, (CH₂)_nCOR¹³, (CH₂)_nSR¹¹, (CH₂)_nNHOA, (CH₂)_nNR¹¹COOR¹³, (CH₂)_nN(R¹¹)CH₂CH₂OR¹³, (CH₂)_nN(R¹¹)CH₂CH₂OCF₃, (CH₂)_nN(R¹¹)C(R¹³)HCOOR⁸, (CH₂)_nN(R¹¹), C(R¹³)HCOR⁸, (CH₂)_nN(COOR¹³)COOR¹⁴, (CH₂)_nN(CONH₂)COOR¹³, (CH₂)_nN(CONH₂)CONH₂, (CH₂)_nN(CH₂COOR¹³)COOR¹⁴, (CH₂)_nN(CH₂CONH₂)COOR¹³,

- 132 -

$(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$,
 $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,

5 X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h-Q-(CHR^{12})_l$, wherein

10 Q is selected from a group consisting of O, S, N-R¹⁵,
 $(CHal_2)_j$, $(O-CHR^{18})_j$, $(CHR^{18}-O)_j$, $CR^{18}=CR^{19}$, $(O-CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}-O)_j$, C=O, C=NR¹⁵,
15 CH(OR¹⁵), C(OR¹⁵)(OR²⁰), C(=O)N(R¹⁵), N(R¹⁵)C(=O),
 CH=N-NR¹⁵, S=O, SO₂, SO₂NR¹⁵ and NR¹⁵SO₂,
 wherein

20 h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6,
 preferably 0, 1, 2 or 3 and

 j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

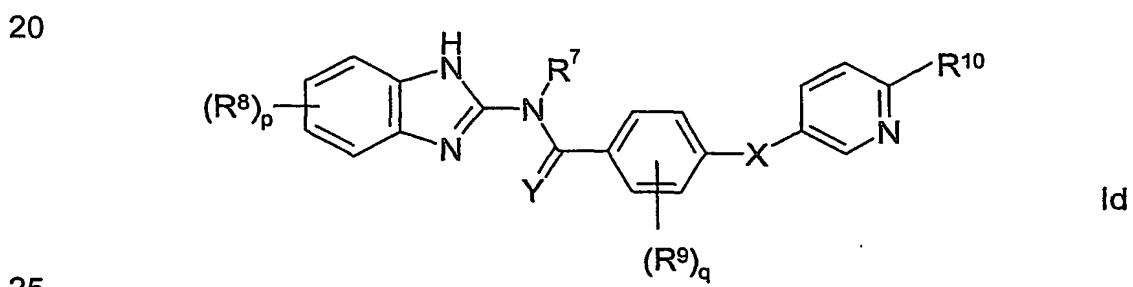
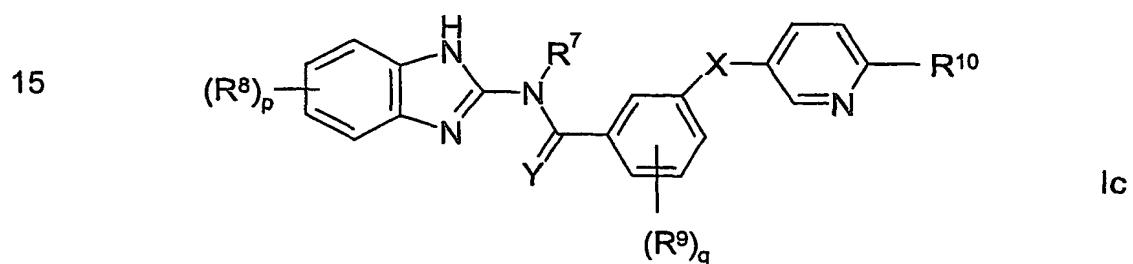
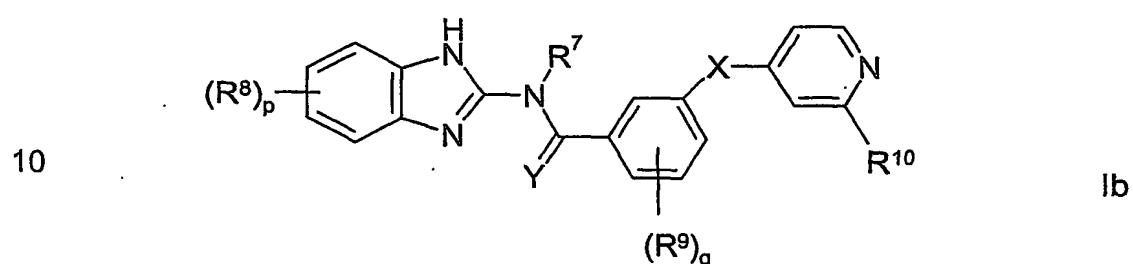
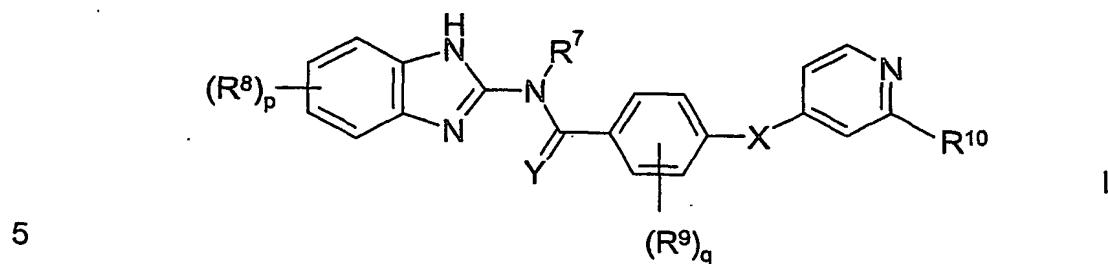
25 p is 1, 2, 3 or 4, preferably 1, 2 or 3, and

 r is 0, 1, 2, or 3, preferably 0, 1 or 2;

 and the physiologically acceptable derivatives, salts and solvates
 thereof.

30 3. Benzimidazole derivative according to claim 1 or 2, selected from the
 compounds of the formulae Ia, Ib, Ic and Id,

- 133 -



wherein

R^7 , R^8 , p , X , Y , R^9 and q are as defined in claims 1 or 2, and R^{10} is H
or as defined in claims 1 or 2;

30
and the physiologically acceptable derivatives, salts and solvates
thereof.

4. Benzimidazole derivative according to claim 3, additionally comprising one or two substituents selected from the group consisting of $O(CH_2)_nNR^{11}R^{12}$, $NR^{11}(CH_2)_nNR^{11}R^{12}$, $O(CH_2)_nOR^{12}$ and $NR^{11}(CH_2)_nOR^{12}$,
5 wherein
 R^{11} , R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,
10 R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7-membered heterocyclohex which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S, and
15 n is 1, 2, 3, 4, 5 or 6.

15 5. Benzimidazole derivative according to one of the claims 1 to 4, selected from the compounds (1) to (78) of table 1; and the physiologically acceptable derivatives, salts and solvates thereof.

20 6. Benzimidazole derivative according to one of the claims 1 to 5 as a medicament.

25 7. Benzimidazole derivative according to one of the claims 1 to 5 as a kinase inhibitor.

8. Benzimidazole derivative according to claim 7, characterized in that the kinases are selected from raf-kinases and VEGFR kinases.

30 9. Pharmaceutical composition, characterized in that it contains one or more compounds according to one of the claims 1 to 5.

- 135 -

10. Pharmaceutical composition according to claim 9, characterised in that it contains one or more additional compounds, selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5.
11. Process for the manufacture of a pharmaceutical composition, characterised in that one or more compounds according to one of the claims 1 to 5 and one or more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to one of the claims 1 to 5, is processed by mechanical means into a pharmaceutical composition that is suitable as dosageform for application and/or administration to a patient.
12. Use of a compound according to one of the claims 1 to 5 as a pharmaceutical.
13. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.
14. Use of a compound according to one of the claims 1 to 5 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
15. Use according to claim 13 or 14, characterised in that the disorders are caused, mediated and/or propagated by kinases selected from raf-kinases and VEGFR kinases.
- 30 16. Use according to claim 13, 14 or 15, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.

- 136 -

17. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is cancer.
- 5 18. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is noncancerous.
- 10 19. Use according to claim 13, 14, 15, 16 or 18, characterised in that the noncancerous disorders are selected from the group consisting of infection, psoriasis, arthritis, inflammation, endometriosis, scarring, beginin prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
- 15 20. Use according to one of the claims 13 to 17, characterised in that the disorders are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia
- 20 21. Use according to one of the claims 13 to 16 and 18, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases.
- 25 30 22. Use according to one of the claims 13 to 18, characterised in that the disorders are selected from the group consisting of rheumatoid arthritis, inflammation, autoimmune disease, chronic obstructive

- 137 -

pulmonary disease, asthma, inflammatory bowel disease, fibrosis, atherosclerosis, restenosis, vascular disease, cardiovascular disease, inflammation, renal disease and angiogenesis disorders.

5 23. Use of a compound according to one of the claims 1 to 5 as a kinase inhibitor.

10 24. Use according to claim 23, characterised in that the kinase is one or more raf-kinases, selected from the group consisting of A-Raf, B-Raf and Raf-1.

15 25. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.

20 26. Method according to claim 25, characterised in that the one or more compounds according to one of the claims claim 1 to 5 are administered as a pharmaceutical composition according to claim 9 or 10.

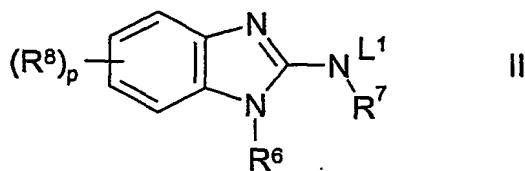
25 27. Method for the treatment and/or prophylaxis of disorders according to claim 25, characterised in that the disorders are as defined in one of the claims 15 to 22.

30 28. Method for the treatment according to claim 27, characterised in that the disorders is cancerous cell growth mediated by one or more kinases.

29. Method for producing compounds of formula I, characterised in that

30 a) a compound of formula II

- 138 -



5

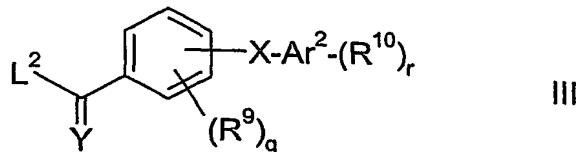
wherein

10 L¹ is H or a metal ion, and R⁶, R⁷, R⁸ and p are as defined in claim
1,

is reacted

b) with a compound of formula III,

15



20

wherein

25 L² is Cl, Br, I, OH, an esterified OH-group or a diazonium moiety,
and Y, R⁹, q, X, Ar², R¹⁰ and r are as defined in claim 1,

and optionally

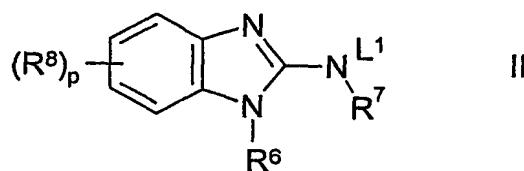
c) isolating and/or treating the compound of formula I obtained by
said reaction with an acid, to obtain the salt thereof.

30

30. Compound of formula II,

- 139 -

5



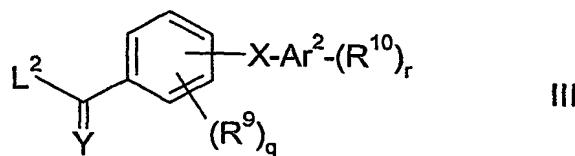
wherein

10

L^1 is H or a metal ion, and R^6 , R^7 , R^8 and p are as defined in claim 1.

31. Compound of formula III,

15



20

wherein

L^2 is Cl, Br, I, OH, an esterified OH-group or a diazonium moiety, and Y , R^9 , q , X , Ar^2 , R^{10} and r are as defined in claim 1.

25

30